1. General Information

ID 136-53-8

Date December 06, 2004

201-15761B1

1.0 SUBSTANCE INFORMATION

Generic Name	:	Hexanoic acid, 2-ethyl, zinc salt
Chemical Name	:	Hexanoic acid, 2-ethyl, zinc salt
CAS Registry No.	:	136-53-8
Component CAS Nos.	:	
EINECS No.	:	205-251-1
Structural Formula	:	$C_{16}H_{30}O_4Zn$
Molecular Weight	:	351.8006
Synonyms and Trade names	:	Zinc 2-ethylhexanoate; ethylhexanoic acid zinc salt; Therm-Chek, ZINC HEX-CHEM
References	:	http://www.chemfinder.com

2.1 MELTING POINT

Type	:	Melting Point/Melting Range
Guideline/method	:	OECD No. 102 EEC Directive 92/69, A.1 EPA OPPTS Guideline 830.7100
Value	:	-47 °C±1°C
Decomposition	:	
Sublimation	:	
Year	:	2003
GLP	:	Yes
Test substance	:	Hexanoic Acid, 2-Ethylhexyl, Zinc salt, 99%
Method	:	Combination of thermal analysis using a calorimeter and visual test for physical state change
Method detail	:	
Result	:	The freezing temperature for Hexanoic Acid, 2-Ethylhexyl, Zinc salt was determined to be -47 °C±1°C
Remark	:	Testing was conducted on triplicate samples
Reliability	:	(1) Reliable without restrictions
Reference	:	Determination of the Melting Point/Melting Range of Hexanoic Acid, 2-Ethylhexyl, Zinc salt RCC Study Number 849075, RCC, Ltd., Itingen, Switzerland, August 21, 2003.

2.2 BOILING POINT

Type	:	Boiling Point/Boiling Range
Guideline/method	:	OECD No. 103 EEC Directive92/69, A.2. EPA OPPTS Guideline 830.7220
Value	:	> 400 °C
Decomposition	:	
Year	:	2003
GLP	:	Yes
Test substance	:	Hexanoic Acid, 2-Ethylhexyl, Zinc salt, 99%
Method	:	Combination of thermal analysis using a calorimeter and visual test for physical state change and weight change.
Method detail	:	
Result	:	In the temperature range of 25 to 400°C, no boiling activity (endothemic peaks using thermal analysis) could be observed.
Remark	:	The absence of a boiling point or range at these temperatures was confirmed in a duplicate experiment.
Reliability	:	(1) Reliable without restrictions
Reference	:	Determination of the Boiling Point/Boiling Range of Hexanoic Acid, 2-Ethylhexyl, Zinc salt RCC Study Number 849076, RCC, Ltd., Itingen, Switzerland, August 21, 2003.

2.3 DENSITY

Type	:	Not stated
Guideline/method	:	Not stated

Value	:	1.180
Year	:	Not stated
GLP	:	No
Test substance	:	Hexanoic Acid, 2-Ethylhexyl, Zinc salt, 99%
Method	:	Not stated
Method detail	:	
Result	:	The density of Hexanoic Acid, 2-Ethylhexyl, Zinc salt, is reported to be 1.180
Remark	:	
Reliability	:	(2) Reliable with restrictions
Reference		MSDS dated December, 2003

2.4 VAPOR PRESSURE

Type	:
Guideline/method	:
Value	:
Decomposition	:
Year	:
GLP	:
Test substance	:
Method	:
Method detail	:
Result	:
Remark	:
Reliability	:
Reference	:

2.5 PARTITION CONSTANT

Type	:
Guideline/method	:
Value	:
pH value	:
Year	:
GLP	:
Test substance	:
Method	:
Method detail	:
Result	:
Remark	:
Reliability	:
Reference	:

2.6.1 SOLUBILITY IN WATER

Type	:	Water solubility
Guideline/method	:	OECD No. 15 EEC Directive 92/69, A. 6. EPA OPPTS Guideline 830.7840
Value	:	20.2 mg/l @20ºC
pH value	:	6.6 to 7.2
concentration	:	

Temperature effects	:	20 ± 0.5ºC
Examine different pol.	:	
PKa	:	6.99 at 20°C
Description	:	
Stable	:	
Deg. product	:	
Year	:	2004
GLP	:	Yes
Test substance	:	Hexanoic Acid, 2-Ethylhexyl, Zinc salt, 99%
Deg. products CAS#	:	
Method	:	The column elution method was used to determine the saturation concentration of the test item in pure water at 20°C. Sampling of the column eluate was by atomic absorption specotroscopy.
Result	:	The water solubility of Hexanoic Acid, 2-Ethylhexyl, Zinc salt was 20.2 mg/l @20ºC based on a measured concentration of 3.76 mg Zn/l (±0.27mg Zn/l)
Remark	:	Twelve replicate elutions and analyses were conducted and all results differed by less than 30%**.**
Reliability	:	(1) Reliable without restrictions
Reference	:	Determination of the Water Solubility of Hexanoic Acid, 2-Ethylhexyl, Zinc salt RCC Study Number 849078, RCC, Ltd., Itingen, Switzerland, July 21, 2004.

2.7 FLASH POINT

Type	:	
Guideline/method	:	
Value	:	> 250 °F
Year	:	
GLP	:	
Test substance	:	Mixture of zinc 2-ethylhexanoate (98% by weight) and diethylene glycol monomethyl ether
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	MSDS dated 11/30/00, prepared by The Shepherd Chemical Company

3.1.1 PHOTODEGRADATION

Type		
Guideline/method	:	
Light source	:	
Light spectrum	:	
Relative intensity	:	based on
Spectrum of substance	:	lambda (max, >295nm) epsilon (max) epsilon (295)
Conc. of substance	:	
DIRECT PHOTOLYSIS		
Half-life (t1/2)	:	
Degradation	:	% after
Quantum yield	:	
INDIRECT PHOTOLYSIS		
Sensitizer	:	
Conc. of sensitizer	:	
Rate constant	:	
Degradation	:	
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.1.2 DISSOCIATION

Type	:	Dissociation constant determination
Guideline/method	:	OECD 112
pKa	:	6.99 at 20°C
Year	:	2002
GLP	:	Yes
Test substance	:	Zinc 2-ethylhexanoate, 1% ethylene glycol monomethyl ether, CAS number 136-53-8, lot number F05L03, received from Alfa Aesar Chemical Company. Liquid, purity of 22.39% zinc.
Approximate water solubility	:	100 mg/L as determined visually in preliminary study
Method	:	OECD Guideline 112, Dissociation Constants in Water
Method detail	:	Three replicate samples of zinc 2-ethylhexanoate were prepared at a nominal concentration of 50 mg/L by fortification of degassed water (ASTM Type II) with a 10 mg/mL stock solution of the test substance in methanol. Each sample was titrated against 0.001N sodium hydroxide while maintained at a test temperature of 20±1°C. At least 10 incremental additions were made before the equivalence point and the titration was carried past the equivalence point. Values of pK were calculated for a minimum of 10 points on the titration curve. Phosphoric acid and 4-nitrophenol were used as reference substances.
Result	:	Mean (N = 3) pKa value was 6.99 (SD = 0.0704) at 20°C
Remark	:	The results indicate that dissociation of the test substance will occur at environmentally-relevant pH values (approximately neutral) and at

physiologically-relevant pH values (approximately 1.2).

Reliability : [1] Reliable without restriction.

Reference : Lezotte, F.J. and W.B. Nixon, 2002. Determination of the dissociation constant of zinc 2-ethylhexanoate, 1% ethylene glycol monomethyl ether, Wildlife International, Ltd. Study No. 534C-102, conducted for the Metal Carboxylates Coalition.

3.2.1 MONITORING DATA

Type of measurement :
Media :
Concentration : mg/l
Substance measured :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.3.1 TRANSPORT (FUGACITY)

Type :
Media :
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Year :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.5 BIODEGRADATION

Type :
Guideline/method :
Inoculum :
Concentration : related to
related to
Contact time :
Degradation : (±) % after day(s)
Result :
Kinetic of test subst. : % (specify time and % degradation)
%
%
%
%
Control substance :
Kinetic : %
%

Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.7 BIOCONCENTRATION

Type	:	
Guideline/method	:	
Species	:	
Exposure period	:	at °C
Concentration	:	
BCF	:	
Elimination	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

4.1 ACUTE TOXICITY TO FISH

Type	:
Guideline/method	:
Species	:
Exposure period	:
NOEC	:
LC0	:
LC50	:
LC100	:
Other	:
Other	:
Other	:
Limit test	:
Analytical monitoring	:
Year	:
GLP	:
Test substance	:
Method	:
Method detail	:
Result	:
Remark	:
Reliability	:
Reference	:

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:
Guideline/method	:
Species	:
Exposure period	:
NOEC	:
EC0	:
EC50	:
EC100	:
Other	:
Other	:
Other	:
Limit test	:
Analytical monitoring	:
Year	:
GLP	:
Test substance	:
Method	:
Method detail	:
Result	:
Remark	:
Reliability	:
Reference	:

4.3 TOXICITY TO AQUATIC PLANTS (E.G., ALGAE)

Type	:
Guideline/method	:
Species	:
Endpoint	:
Exposure period	:

NOEC	:
LOEC	:
EC0	:
EC10	:
EC50	:
Other	:
Other	:
Other	:
Limit test	:
Analytical monitoring	:
Year	:
GLP	:
Test substance	:
Method	:
Method detail	:
Result	:
Remark	:
Reliability	:
Reference	:

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In vitro/in vivo	:	
Type	:	
Guideline/method	:	
Species	:	
Number of animals	:	
Males	:	
Females	:	
Doses	:	
Males	:	
Females	:	
Vehicle	:	
Route of administration	:	
Exposure time	:	
Product type guidance	:	
Decision on results on acute tox. tests	:	
Adverse effects on prolonged exposure	:	
Half-lives	:	1st.: 2nd.: 3rd.:
Toxic behavior	:	
Deg. product	:	
Deg. products CAS#	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

5.1.1 ACUTE ORAL TOXICITY

Type	:	Acute Oral (LD50) Toxicity
Guideline/Method	:	
Species	:	Rat
Strain	:	Sherman-Wistar albino
Sex	:	Male and female
Number of animals	:	10 per dose (5 male, 5 female)
Vehicle	:	
Doses	:	1.58, 2.0, 2.51, 3.16, 3.98, 5.01 and 6.32 g/kg
LD50	:	Males: 3.7 g/kg (95% CI: 3.04 – 4.62 g/kg). Females: 3.55 g/kg (95% CI: 2.95 – 4.26 g/kg)
Year	:	1980
GLP	:	Not reported
Test substance	:	Zinc octoate, 18%, Lot # 150. Described as zinc 2-ethylhexanoate 79.1%, mineral spirits 20.9% (CAS # 8032-32-4). Negligibly soluble in water, soluble in organic solvents. Density 1.022 g/mL.
Method	:	Tested in accordance with Federal Hazardous Substances Act, 16 CFR Section 1500.3.
Method detail	:	Animals (200 - 300 g) fasted overnight (food only) prior to dosing, weighed and administered the test material (as received) via intragastric intubation.

Observed for 14-days post-exposure.

Result : LD50 for Males: 3.7 g/kg (95% CI: 3.04 – 4.62 g/kg). LD50 for Females: 3.55 g/kg (95% CI: 2.95 - 42.6 g/kg). For males: 3/5, 4/5 and 5/5 rats died at the three highest doses, respectively. One rat died at 2.51 g/kg and one rat died at 3.16 g/kg. For females: 2/5, 3/5, 5/5, and 5/5 rats died at the four highest doses, respectively. For both sexes, within 1-2 hr following dosing, animals displayed numerous symptoms (slight ataxia, depression, ruffled, and drooling at lower doses; semi-comatose and death higher doses). Animals, which survived, recovered fully after 1-4 days. Gross necropsies were unremarkable.

Remark :

Reliability : [2] Reliable with restrictions. Basic data provided, exposure conditions not fully described. Comparable to guideline.

Reference : Biosearch, Inc., Philadelphia, PA. (Study no. 80-1975A), study conducted for Tenneco Chemicals, Inc., Saddle Brook, NJ.

5.1.2 ACUTE INHALATION TOXICITY

Type : Limit Test

Guideline/method :

Species : Rat

Strain : Albino

Sex : Male and female

Number of animals : 10 (5 male and 5 female)

Vehicle :

Doses : One concentration, 23.2 mg/L of a 25% w/v suspension in mineral spirits. Median particle diameter measured to ensure a respirable dose was received.

Exposure time : 1 hour

LC50 : > 23.2 mg/L (maximum attainable nominal concentration)

Year : 1980

GLP : Not reported

Test substance : Zinc octoate 18% (Lot # 150), prepared and used as a 25% w/v suspension in mineral spirits.

Method :

Method detail : Animals (205 – 210 g, average) were exposed to the test material inside a 260-L Plexiglas exposure chamber for 1 hour. Presumably whole body exposure, though not described in report. An aerosol was generated by a jet collision nebulizer; air was passed through the test material and into the chamber at 20 L/min., at 70ºF. Test material concentration was measured and determined to be 23.2 mg/L (determined by weighing the flask containing the aerosol before and after exposure). Particle size, determined for 5 minutes midway through the exposure period, was calculated to be 1.1 microns MMD (mass median diameter). Animals observed for 14 days post-exposure

Result : No mortality, no toxicity, and no adverse gross necropsy findings

Remark :

Reliability : [2] Reliable with restrictions. Basic data provided. Exposure conditions not described, duration of exposure and determination of measured test concentrations less than current guidelines require.

Reference : Biosearch, Inc., Philadelphia, PA. (Study no. 80-1975A), conducted for Tenneco Chemicals, Inc., Saddle Brook, NJ.

5.1.3 ACUTE DERMAL TOXICITY

Type : Limit Test

Guideline/method :

Species	:	Rabbit
Strain	:	Albino
Sex	:	Male and female
Number of animals	:	Six (3 male and 3 female)
Vehicle	:	
Doses	:	One dose, 5 g/kg
LD50	:	> 5 g/kg
Year	:	1980
GLP	:	Not reported
Test substance	:	Zinc octoate, 18%, Lot # 150. Described as zinc 2-ethylhexanoate 79.1%, mineral spirits 20.9% (CAS # 8032-32-4). Negligibly soluble in water, soluble in organic solvents
Method	:	Tested in accordance with Federal Hazardous Substances Act, 16 CFR Section 1500.40.
Method detail	:	Animals (2-3 kg) had their backs clipped free of hair and abraded 24 hours prior to dose administration. Each animal was weighed and the appropriate amount of test material applied to the back, covered with gauze and impervious damming. Dressings were removed after 24 hours, excess material removed, and backs wiped clean. Animals observed for 14 days post-exposure.
Result	:	No mortality or toxicity. No adverse gross necropsy findings
Remark	:	
Reliability	:	[2] Reliable with restrictions. Basic data provided. Exposure conditions not fully described, size of area of application not mentioned. Comparable to guideline.
Reference	:	Biosearch, Inc., Philadelphia, PA. (Study no. 80-1975A), conducted for Tenneco Chemicals, Inc., Saddle Brook, NJ.

5.2.1 SKIN IRRITATION

Type	:	Contact dermal irritation/sensitization
Guideline/method	:	
Species	:	Guinea pig, albino
Strain	:	
Sex	:	Male, weighing 300 – 400 g
Concentration	:	
Exposure	:	
Exposure time	:	
Number of animals	:	10
Vehicle	:	
Classification	:	
Year	:	1980
GLP	:	Not reported
Test substance	:	Zinc octoate, 18%, Lot # 150.
Method	:	
Method detail	:	A 0.5 mL portion of material was applied to the intact skin test sites on the guinea pigs. A gauze patch was placed over the treated area and an impervious material was wrapped snugly around the trunks of the animals to hold the patch in place. After 24 hours, the patch was removed, the animals allowed to rest for 1 day, and another application was made to the same skin site. This sequence was repeated for a total of 10 applications, after which time the animals were given a two week rest period. Subsequently a challenge application was put on skin sites differing from the original test sites. The challenge application remained on for 24 hours. The sites were examined for irritation using the Draize method of scoring, 24 hours after each induction application and 24 and 48 hours after the challenge application.

Result	:	The test substance was a primary skin irritant and a fatiguing agent, but not a sensitizing agent.
Remark	:	
Reliability	:	[2] Reliable with restrictions. Basic data provided. Comparable to guideline.
Reference	:	Biosearch, Inc., Philadelphia, PA. (Study no. 80-1975A), conducted for Tenneco Chemicals, Inc., Saddle Brook, NJ.

5.2.2 EYE IRRITATION

Type	:	Primary eye irritation
Guideline/method	:	
Species	:	Rabbits, young adults
Strain	:	Albino
Sex	:	
Concentration	:	
Dose	:	
Exposure time	:	
Number of animals	:	Six
Vehicle	:	
Classification	:	
Year	:	1980
GLP	:	Not reported
Test substance	:	Zinc octoate, 18%, Lot # 150.
Method	:	
Method detail	:	0.1 mL of the test material was instilled into the right eyes of the animals while the other eye served as the untreated control. The test material was not washed from the eyes. The treated eyes were examined at 1, 2, 3, 5, and 7 days following exposure. Results were scored according to the Draize Scale of Scoring Ocular Lesions.
Result	:	The test substance was not a primary ocular irritant within the definition of the Federal Hazardous Substances Act.
Remark	:	
Reliability	:	[2] Reliable with restrictions. Basic data provided. Comparable to guideline.
Reference	:	Biosearch, Inc., Philadelphia, PA. (Study no. 80-1975A), conducted for Tenneco Chemicals, Inc., Saddle Brook, NJ.

5.4 REPEATED DOSE TOXICITY

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Number of animals	:	
Route of admin.	:	
Exposure period	:	
Frequency of treatment	:	
Post exposure period	:	
Doses	:	
Control group	:	
NOAEL	:	
LOAEL	:	
Other	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	

Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Mutagenicity
Guideline/method	:	
System of testing	:	Ames assay, standard plate assay
Species	:	*Salmonella typhimurium*
Strain	:	TA98, TA100, TA1535, TA1537 and TA1538
Test concentrations	:	1, 10, 100, 500, and 1000 µg/plate, in duplicate. Dissolved in ethanol.
Cytotoxic concentr.	:	
Metabolic activation	:	Conducted both with and without activation. S-9 fraction derived from rats induced with Aroclor 1254 per Ames et al., 1975, Mut. Res. 31:347-364. No further details.
Year	:	1980
GLP	:	No. GLP is mentioned in attached protocol, but report does not include GLP compliance statement
Test substance	:	Zinc octoate 18%, Lot No. 150
Method	:	Followed method of Ames et. al.
Method detail	:	0.1 mL aliquots of test material at 5 concentrations were used. Positive controls and vehicle controls (ethanol) included. Plates incubated for 48 hours at 37ºC and number of colonies compared to background. No further details provided.
Result	:	Negative. Test material did not induce a significant increase in the number of revertant colonies over that shown in the solvent control plates for all strains of *S. typhimurium* tested, either with or without activation. Mutagenic index of all five strains was less than 2.0. Positive controls produced the expected response.
Remark	:	
Reliability	:	[2] Reliable with restrictions. Basic data provided. Comparable to guideline.
Reference	:	Van Goethem, D., 1980. Evaluation of zinc octoate in the *Salmonella*/Microsome (Ames) assay. Study conducted for Tenneco Chemicals, Inc. by Midwest Research Institute, Kansas City, MO (Study No. 4822-E).

Type	:	Mutagenicity
Guideline/method	:	
System of testing	:	Bacterial DNA damage or repair assay
Species	:	*Escherichia coli*
Strain	:	W3110 (pol A^+) and its DNA polymerase deficient derivative p3478 (pol A^-)
Test concentrations	:	5, 10, 50, 100, and 500 µg/mL, in duplicate. Dissolved in DMSO.
Cytotoxic concentr.	:	
Metabolic activation	:	With and without. Activation with S-9 from Aroclor 1254 induced rat liver per Ames al., 1975, Mut. Res. 31:347-364 .
Year	:	1981
GLP	:	No. GLP is mentioned in attached protocol, but report does not include GLP compliance statement
Test substance	:	Zinc octoate 18%, Lot No. 150
Method	:	Followed method of Rosenkranz et al. (1971).
Method detail	:	Test material (5 concentrations) applied to cells in culture. Vehicle controls (DMSO) included. Positive controls included (N-methyl-N'-nitrosoguanidine at 2 ug/mL without activation and 2-aminofluorene at 200 ug/mL with activation). Bacteria (10^4) of each strain were exposed to the test material

		for 1 hour at 37ºC. Then 0.1 mL aliquots were removed and plated on agar, with and without activation, incubated for 18 hours at 37ºC and the number of viable cells determined.
Result	:	Negative. No dose-response was observed and there was no decrease in survival index (ratio of pol A^- to pol A^+ survivors), with or without activation. Survival index at all nonprecipitating dose levels was greaten than 0.80. Noted that two highest concentrations (with and without activation) caused a white precipitate to form, hence data from these concentrations not useful.
Remark	:	
Reliability	:	[2] Reliable with restrictions. Basic data provided. Comparable to guideline.
Reference	:	Van Goethem, D., 1981. Evaluation of zinc octoate, 18%, in the *E. coli* DNA Repair-Suspension Assay. Study conducted for Tenneco Chemicals, Inc. by Midwest Research Institute, Kansas City, MO (Study No. 4822-E).

5.6 GENETIC TOXICITY 'IN VIVO'

Type	:
Guideline/method	:
Species	:
Strain	:
Sex	:
Route of admin.	:
Exposure period	:
Doses	:
Year	:
GLP	:
Test substance	:
Method	:
Method detail	:
Result	:
Remark	:
Reliability	:
Reference	:

5.8.2 DEVELOPMENTAL TOXICITY

Type	:
Guideline/method	:
Species	:
Strain	:
Sex	:
Route of admin.	:
Exposure period	:
Frequency of treatment	:
Duration of test	:
Doses	:
Control group	:
NOAEL maternal tox.	:
NOAEL teratogen.	:
Other	:
Other	:
Other	:
Year	:
GLP	:
Test substance	:
Method	:
Method detail	:
Result	:

Remark	:
Reliability	:
Reference	:

5.8.3 TOXICITY TO REPRODUCTION

Type	:
Guideline/method	:
In vitro/in vivo	:
Species	:
Strain	:
Sex	:
Route of admin.	:
Exposure period	:
Frequency of treatment	:
Duration of test	:
Doses	:
Control group	:
Year	:
GLP	:
Test substance	:
Method	:
Method detail	:
Result	:
Remark	:
Reliability	:
Reference	:

6.0 OTHER INFORMATION

6.1. CARCINOGENICITY

1.0 SUBSTANCE INFORMATION

Generic Name	:	Zinc chloride
Chemical Name	:	Zinc dichloride
CAS Registry No.	:	7646-85-7
Component CAS Nos.	:	
EINECS No.	:	231-592-0
Structural Formula	:	$ZnCl_2$
Additional description	:	
Molecular Weight	:	136.29
Synonyms and Tradenames	:	Zinc (II) chloride; Butter of zinc; zinc butter; RTECS ZH1400000
References	:	ATSDR, 2003 (Agency for Toxic Substances and Disease Registry, Draft Toxicological Profile for Zinc, September 2003)

2.1 MELTING POINT

Type	:	
Guideline/method	:	
Value	:	290 °C
Decomposition	:	
Sublimation	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	2 (reliable with restrictions): Source is well established data compendium.
Reference	:	O'Neil, M.J., Smith, A., Heckelman, P.E., and J.R. Obenchain (eds.). 2002. The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Ed. Merck & Co., Inc., Whitehouse Station, NJ.

2.2 BOILING POINT

Type	:	
Guideline/method	:	
Value	:	732 °C
Decomposition	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	2 (reliable with restrictions): Source is well established data compendium.
Reference	:	O'Neil, M.J., Smith, A., Heckelman, P.E., and J.R. Obenchain (eds.). 2002. The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Ed. Merck & Co., Inc., Whitehouse Station, NJ.

2.3 DENSITY

Type	:	
Guideline/method	:	
Value	:	2.907 at 25°C
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	2 (reliable with restrictions): Source is well established data compendium.
Reference	:	O'Neil, M.J., Smith, A., Heckelman, P.E., and J.R. Obenchain (eds.). 2002. The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Ed. Merck & Co., Inc., Whitehouse Station, NJ.

2.4 VAPOR PRESSURE

Type	:	
Guideline/method	:	
Value	:	
Decomposition	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	Expected to be very low based on melting point and boiling point data.
Reliability	:	
Reference	:	

2.5 PARTITION COEFFICIENT

Type	:	
Guideline/method	:	
Partition coefficient	:	
Log Pow	:	
pH value	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	Not applicable – compound dissociates and ionizes in water
Reliability	:	
Reference	:	

2.6.1 SOLUBILITY IN WATER

Type	:	
Guideline/method	:	
Value	:	4.32 X 10^6 mg/L at 25 °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
PKa	:	at °C
Description	:	
Stable	:	
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	2 (reliable with restrictions): Source is well established data compendium.
Reference	:	O'Neil, M.J., Smith, A., Heckelman, P.E., and J.R. Obenchain (eds.). 2002. The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Ed. Merck & Co., Inc., Whitehouse Station, NJ.

2.7 FLASH POINT

Type	:	
Guideline/method	:	
Value	:	Not flammable
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.1.1 PHOTODEGRADATION

Type		
Guideline/method	:	
Light source	:	
Light spectrum	:	
Relative intensity	:	based on
Spectrum of substance	:	lambda (max, >295nm) :
		epsilon (max) :
		epsilon (295) :
Conc. of substance	:	at °C
DIRECT PHOTOLYSIS		
Halflife (t1/2)	:	
Degradation	:	% after
Quantum yield	:	
INDIRECT PHOTOLYSIS		
Sensitizer	:	
Conc. of sensitizer	:	
Rate constant	:	
Degradation	:	
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	Not applicable – the metal will not degrade
Reliability	:	
Reference	:	

3.2.1 MONITORING DATA

Type of measurement	:	
Media	:	
Concentration	:	mg/l
Substance measured	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.3.1 TRANSPORT (FUGACITY)

Type	:	
Media	:	
Air	:	% (Fugacity Model Level I)
Water	:	% (Fugacity Model Level I)
Soil	:	% (Fugacity Model Level I)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	% (Fugacity Model Level II/III)
Year	:	
Test substance	:	

Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.5 BIODEGRADATION

Type :
Guideline/method :
Inoculum :
Concentration : related to
related to
Contact time :
Degradation : (±) % after day(s)
Result :
Kinetic of test subst. : % (specify time and % degradation)
%
%
%
%
Control substance :
Kinetic : %
%
Deg. product :
Year :
GLP :
Test substance :
Deg. products CAS# :
Method :
Method detail :
Result :
Remark : Not applicable – the metal will not degrade
Reliability :
Reference :

3.7 BIOCONCENTRATION

Type :
Guideline/method :
Species :
Exposure period : at °C
Concentration :
BCF :
Elimination :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

4.1 ACUTE TOXICITY TO FISH

Type	:	Acute
Guideline/method	:	Flow-through, freshwater
Species	:	Rainbow trout (*Onchorhynchus mykiss*)
Exposure period	:	96 hr
NOEC	:	
LC0	:	
LC50	:	93 – 0.815 µg Zn/L (depending on juvenile life-stage)
LC100	:	
Limit test	:	
Analytical monitoring	:	No
Year	:	1978
GLP	:	No
Test substance	:	Zinc chloride
Method	:	
Method detail	:	The toxicity of zinc chloride to four juvenile stages of rainbow trout (alvins, swim-up fry, parr, smolts) was determined in 96-h flow-through tests.
Result	:	LC50 values varied by life stage with the swim-up fry being the most sensitive.
Remark	:	The bioavailability and resultant aquatic toxicity of zinc chloride is affected by a variety of factors, including water hardness, pH, dissolved organic carbon and temperature. Reported 96-h LC50 values for zinc chloride (expressed as zinc) for various species of fish include 0.29 mg Zn/L and 0.42 mg Zn/L for bluegill (*Lepomis macrochirus*); 0.093 – 2.17 mg Zn/L for rainbow trout (*Onchorhynchus mykiss*), 0.45 - 2.25 mg Zn/L for common mirror-colored carp (*Cyprinus carpio*) and 1.70 mg Zn/L for sheepshead minnow (*Cyprinodon variegatus*) (U.S. EPA, ECOTOX database, 2003).
Reliability	:	2 (reliable with restrictions): Comparable to guideline study with adequate documentation.
Reference	:	Chapman, G.A. 1978. Toxicities of cadmium, copper, and zinc to four juvenile stages of Chinook and steelheads. Trans. Am. Fish. Soc., 107(6):841-847.

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	Acute
Guideline/method	:	Flow-through, freshwater
Species	:	*Daphnia magna*
Exposure period	:	48 hr
NOEC	:	
EC0	:	
EC50	:	799 µg Zn/L
EC100	:	
Limit test	:	
Analytical monitoring	:	
Year	:	1982
GLP	:	No
Test substance	:	Zinc chloride
Method	:	Flow-through
Method detail	:	
Result	:	
Remark	:	The bioavailability and resultant aquatic toxicity of zinc chloride is affected by a variety of factors, including water hardness, pH, dissolved organic carbon and temperature. Reported 48-h EC50 values for zinc chloride (expressed as zinc) for *Daphnia magna* include 0.33, 0.52, 0.66 and 0.80

		mg Zn/L (U.S. EPA, ECOTOX database, 2003). For several crustaceans, including *Daphnia magna*, *Ceriodaphnia dubia*, and *Ceriodaphnia reticulata*, reported 48-h EC50 values ranged from 0.068 to 0.86 mg Zn/L, for zinc tested as zinc chloride or zinc sulfate.
Reliability	:	2 (reliable with restrictions): Comparable to guideline study with adequate documentation.
Reference	:	Attar, E.N. and E.J. Maly. 1982. Acute toxicity of cadmium, zinc, and cadmium-zinc mixtures to *Daphnia magna*. Arch. Environ. Contam. Toxicol., 11(3):291-296.

4.3 TOXICITY TO AQUATIC PLANTS (E.G., ALGAE)

Type	:	Algal growth assay
Guideline/method	:	Static
Species	:	*Selenastrum capricornutum*
Endpoint	:	Growth
Exposure period	:	96 hr
NOEC	:	
LOEC	:	
EC0	:	
EC10	:	
EC50	:	44.7 µg Zn/L
Limit test	:	
Analytical monitoring	:	
Year	:	
GLP	:	No
Test substance	:	Zinc chloride
Method	:	Microplate algal assay
Method detail	:	
Result	:	
Remark	:	The bioavailability and resultant aquatic toxicity of zinc is affected by a variety of factors, including water hardness, pH, dissolved organic carbon and temperature The reported 72-h EC50 for the marine diatom *Skeletonema costatum* was 0.142 mg Zn/L (U.S. EPA, ECOTOX database, 2003).
Reliability	:	2 (reliable with restrictions): Comparable to guideline study with adequate documentation.
Reference	:	Alaise, C., R. Legault, N. Bermingham, R. Van Coillie, and P. Vasseur. 1986. A simple microplate algal assay technique for aquatic toxicity assessment. Toxic. Assess., 1:261-281.

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In vitro/in vivo	:	
Type	:	
Guideline/method	:	
Species	:	
Number of animals	:	
Males	:	
Females	:	
Doses	:	
Males	:	
Females	:	
Vehicle	:	
Route of administration	:	
Exposure time	:	
Product type guidance	:	
Decision on results on acute tox. tests	:	
Adverse effects on prolonged exposure	:	
Half-lives	:	1st: 2nd: 3rd:
Toxic behavior	:	
Deg. product	:	
Deg. products CAS#	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	Zinc is an essential element in nutrition, and is important in membrane stability, in over 300 enzymes, and in the metabolism of proteins and acids. (WHO, 2001, Environmental Health Criteria 221, Zinc). Absorption of zinc in laboratory animals can vary from 10-40% depending upon nutritional status and other ligands in the diet. Absorbed zinc is mainly deposited in muscle, bone, liver, pancreas, kidney and other organs. The biological half-life of zinc ranges from 4 to 50 days in rats depending on the administered dose (WHO, 2001, Environmental Health Criteria 221, Zinc). Increases in zinc concentration in the bodies of experimental animals exposed to zinc are accompanied by reduced levels of copper, suggesting that some of the signs of toxicity ascribed to zinc may be caused by zinc-induced copper deficiency. Moreover, studies have shown that exposure to zinc alters the levels of other essential metals, including iron. Zinc deficiency in animals is characterized by a reduction in growth and cell replication, adverse reproductive and developmental effects, and reduced immunoresponsiveness. (WHO, 2001, Environmental Health Criteria 221, Zinc).
Reliability	:	
Reference	:	

5.1.1 ACUTE ORAL TOXICITY

Type	:	Oral
Guideline	:	Not specified
Species	:	Rat
Strain	:	Sprague-Dawley
Sex	:	Male
Number of animals	:	10 per dose group
Vehicle	:	Water
Doses	:	Not specified
LD50	:	1,100 mg/kg b.w. as $ZnCl_2$ (95% C.I. = 661 – 1,830 mg/kg b.w.) 528 mg/kg b.w. as zinc (95% C.I. = 316 – 875 mg/kg b.w.)
Year	:	1988
GLP	:	No
Test substance	:	Zinc chloride
Method	:	Single doses administered intragastrically.
Method detail	:	Rats weighed 230 – 280 g. Solution concentrations were adjusted so that a 300–g rat received a 1 ml dose. Solutions were adjusted to a pH of between 6.0 and 7.0, using sodium biocarbonate when necessary.
Result	:	Acute LD50 values of zinc chloride were also determined using i.p administration in this study. The toxicity of zinc chloride to rats was much greater after i.p. administration with an LD50 of 58 mg/kg b.w. when expressed as $ZnCl_2$ (95% C.I. = 43 – 79) or 28 mg/kg b.w. when expressed as zinc (95% C.I. = 21 – 38). The much lower toxicity by the oral route of administration suggests a low rate of absorption of zinc chloride from the gastrointestinal tract.
Remark	:	Acute oral toxicity in rodents exposed to zinc compounds is low, and the level at which zinc produces no adverse effect in rats is approximately 160 mg/kg body weight (WHO, 2001, Environmental Health Criteria 221, Zinc). Of the compounds zinc nitrate, zinc sulfate, zinc chloride and zinc acetate, zinc acetate was the most toxic, with oral LD50 values of 237 mg Zn/kg bw (rat) and 86 mg Zn/kg bw (mouse).
Reliability	:	2 (reliable with restrictions): Comparable to guideline study with adequate documentation.
Reference	:	Domingo, J.L., J.M. Llobet, J.I. Paternain, and J. Corbella. 1988. Acute zinc intoxication: comparison of the antidotal efficacy of several chelating agents. Vet. Hum. Toxicol., 30(3): 224-228.

Type	:	Oral
Guideline/Method	:	Not specified
Species	:	Mouse
Strain	:	Swiss
Sex	:	Male
Number of animals	:	10 per dose group
Vehicle	:	Water
Doses	:	Not specified
LD50	:	1,260 mg/kg b.w. as $ZnCl_2$ (95% C.I. = 775 – 2,300 mg/kg b.w.) 605 mg/kg b.w. as zinc (95% C.I. = 370 – 1,099 mg/kg b.w.)
Year	:	1988
GLP	:	No
Test substance	:	Zinc chloride
Method	:	Single doses administered intragastrically.
Method detail	:	Mice weighed 24 – 28 g. Solution concentrations were adjusted so that a 30–g mouse received a 0.21 ml dose. Solutions were adjusted to a pH of between 6.0 and 7.0, using sodium biocarbonate when necessary.
Result	:	Acute LD50 values of zinc chloride were also determined using i.p administration in this study. The toxicity of zinc chloride to mice was much greater after i.p. administration with an LD50 of 91 mg/kg b.w. when

		expressed as $ZnCl_2$ (95% C.I. = 57 – 146) or 44 mg/kg b.w. when expressed as zinc (95% C.I. = 27 – 69). The much lower toxicity by the oral route of administration suggests a low rate of absorption of zinc chloride from the gastrointestinal tract.
Remark	:	
Reliability	:	2, reliable with restrictions: Comparable to guideline study with adequate documentation.
Reference	:	Domingo, J.L., J.M. Llobet, J.I. Paternain, and J. Corbella. 1988. Acute zinc intoxication: comparison of the antidotal efficacy of several chelating agents. Vet. Hum. Toxicol., 30(3): 224-228.

5.1.2 ACUTE INHALATION TOXICITY

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Concentrations	:	
Exposure time	:	
LC50	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	Zinc chloride is a primary ingredient in smoke bombs, resulting in respiratory injury. In a 10-minute inhalation study with rats, zinc chloride aerosol was lethal at concentrations as low as 940 mg Zn/m^3 (Risk Assessment for Zinc Metal, 2001, draft).
Reliability	:	
Reference	:	

5.1.3 ACUTE DERMAL TOXICITY

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
LD50	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	Zinc chloride is reported to cause moderate to severe skin irritation in the rabbit, guinea pig and mouse at 0.48 mg Zn/cm2 while zinc acetate at 7.2

mg Zn/cm^2 was reported to be irritating to the rabbit and mouse but caused no effects in the guinea pig (ATSDR, 1994, Toxicological Profile for Zinc).

Reliability :
Reference :

5.2.1 SKIN IRRITATION

Type :
Guideline/method :
Species :
Strain :
Sex :
Concentration :
Exposure :
Exposure time :
Number of animals :
Vehicle :
Classification :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : Zinc chloride, applied daily as a 1% aqueous solution in an open patch test for 5 days, was severely irritant in rabbits, guinea pigs and mice, inducing epidermal hyperplasia and ulceration. (Lansdown, 1991 as cited in WHO, 2001, Environmental Health Criteria 221, Zinc).
Reliability :
Reference :

5.2.2 EYE IRRITATION

Type :
Guideline/method :
Species :
Strain :
Sex :
Concentration :
Dose :
Exposure time :
Number of animals :
Vehicle :
Classification :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

5.4 REPEATED DOSE TOXICITY

Type	:	28-d Oral
Guideline	:	Not specified
Species	:	Rat
Strain	:	Wistar
Sex	:	Both male and female
Number of animals	:	13 males; 17 females in treatment group
Route of admin.	:	Drinking water
Exposure period	:	4 weeks
Frequency of treatment	:	Continuous
Post exposure period	:	None
Doses	:	11.66 mg Zn/kg b.w./day in males and 12.75 mg Zn/kg b.w./day in females on average from 0.12 mg Zn/cm^3 in water
Control group	:	Yes
NOAEL	:	None
LOAEL	:	12 mg Zn/kg b.w./day
Other	:	
Year	:	1992
GLP	:	No
Test substance	:	Zinc chloride
Method	:	
Method detail	:	Two-month-old Wistar rats of both sexes received zinc chloride in their drinking water for a period of 4 weeks. Liquid consumption was monitored so that the average daily Zn exposure could be calculated. At study termination, rats were weighed, bled, and sacrificed. Hematological indices were determined on blood samples.
Result	:	Zinc treatment had no effect on the survival or body weight gain of exposed rats. Zinc treatment also had no appreciable affect on the composition of bone marrow cells. However, erythrocytes counts and hemoglobin levels in the peripheral blood were significantly decreased in Zn-exposed males and females compared to controls, while the numbers of leukocytes, neutrophils, and lymphocytes in male rats were increased compared to controls.
Remark	:	Long-term oral exposure to zinc compounds indicates the target organs of toxicity to be the hematopoeitic system in rats, ferrets and rabbits; the kidney in rats and ferrets; and the pancreas in mice and ferrets (WHO, 2001, Environmental Health Criteria 221, Zinc). Zinc acetate given to rats in water over three months yielded NOAEL values of 95 to 191 mg Zn/kg/d. During a 13-week exposure to zinc sulfate via the diet, NOAEL values for the rat ranged from 53 to 565 mg Zn/kg/day and for the mouse were 104 mg Zn/kg/d, based upon various parameters. (ATSDR, 2003, Draft Toxicological Profile for Zinc).
Reliability	:	2 (reliable with restrictions): Comparable to guideline study with adequate documentation.
Reference	:	Zaporowska, H. and W. Wasilewski. 1992. Combined effect of vanadium and zinc on certain selected haematological indices in rats. Comp. Biochem. Physiol., 103C: 143-147.

Type	:	13-week Oral
Guideline/method	:	Not specified
Species	:	Rat
Strain	:	Wistar
Sex	:	Male and female
Number of animals	:	12 of each sex per treatment group
Route of admin.	:	Diet
Exposure period	:	13 wk
Frequency of treatment	:	Continuous

Post exposure period	:	None
Doses	:	0, 300, 3,000, or 30,000 ppm in diet (equivalent to an average daily intake of 23.2, 234, or 2,514 mg $ZnSO_4$/kg/d in males and 24.5, 243, or 2,486 mg $ZnSO_4$/kg/d in females
Control group	:	Yes, for both males and females
NOAEL	:	3,000 ppm in diet (equivalent to approximately 234 mg $ZnSO_4$/kg/d in males and 243 mg $ZnSO_4$/kg/d in females)
LOAEL	:	30,000 ppm in diet (equivalent to approximately 2,514 mg $ZnSO_4$/kg/d in males and 2,486 mg $ZnSO_4$/kg/d in females)
Other	:	
Year	:	1981
GLP	:	No
Test substance	:	$ZnSO_4 \cdot 7H_2O$
Method	:	
Method detail	:	Groups of male and female rats (12 each) were feed diets containing zinc sulfate for 13 weeks. Animals were observed daily for clinical signs of toxicity and weighed weekly. Feed and water intake was measured twice per week. Prior to study termination, blood samples were collected and analyzed for hematological and biochemical parameters. Following necropsy, gross pathological and histopathological examinations were conducted on selected target organs and tissues. Organs weights were also determined.
Results	:	No compound-related mortality was observed at any dose level. The only clinical signs of toxicity were behavioral (removal of chow from the feeding container) and confined to the highest feeding level (30,000 ppm). At the highest dose level, food consumption, water intake and growth were reduced, particularly in males. A moderate reduction in the total leukocyte count was observed in both sexes in the high dose groups, whereas males in this group also showed slightly decreased hematocrit and hemoglobin levels. GOT and GPT concentrations were decreased in all male groups but there was no dose-response trend. Total protein, cholesterol and calcium in the blood were decreased in high dose males, whereas only calcium was elevated in high dose females. Necropsy results indicated no remarkable gross lesions in rats at any dose level, although the weights (both absolute and relative) of the livers and kidneys of the males in the 30,00 ppm group showed a slight to moderate decrease. Histopathological examinations showed pancreatic lesions attributable to treatment in the high dose groups. Lesions consisted of degeneration and necrosis of the acinar cells, clarification of centroacinar cells, and interstitial fibrosis.
Remark	:	While not conducted on the zinc chloride salt, the results of this study on hydrated zinc sulfate are considered relevant for assessing the potential hazard of the chloride because both salts are soluble and expected to have a similar bioavailability and toxicity. In general, after oral or dermal exposure, the toxicities of all zinc compounds are comparable (ATSDR, 2003. Draft Toxicological Profile for Zinc).
Reliability	:	2 (reliable with restrictions): Comparable to guideline study with adequate documentation.
Reference	:	Maita, K., M. Hirano, K. Mitsumori, K. Takahashi, and Y. Shirasu. 1981. Subacute toxicity studies with zinc sulfate in mice and rats. J. Pesticide Sci., 6: 327-336.
Type	:	13-week Oral
Guideline/method	:	Not specified
Species	:	Mouse
Strain	:	ICR (specific pathogen-free)
Sex	:	Male and female
Number of animals	:	12 of each sex per treatment group

Route of admin.	:	Diet
Exposure period	:	13 wk
Frequency of treatment	:	Continuous
Post exposure period	:	None
Doses	:	0, 300, 3,000, or 30,000 ppm in diet (equivalent to an average daily intake of 42.7, 458, or 4,927 mg $ZnSO_4$/kg/d in males and 46.4, 479, or 4,878 mg $ZnSO_4$/kg/d in females
Control group	:	Yes, for both males and females
NOAEL	:	3,000 ppm in diet (equivalent to approximately 458 mg $ZnSO_4$/kg/d in males and 479 mg $ZnSO_4$/kg/d in females)
LOAEL	:	30,000 ppm in diet (equivalent to approximately 4,927 mg $ZnSO_4$/kg/d in males and 4,878 mg $ZnSO_4$/kg/d in females)
Other	:	
Year	:	1981
GLP	:	No
Test substance	:	$ZnSO_4 \cdot 7H_2O$
Method	:	
Method detail	:	Groups of male and female mice (12 each) were feed diets containing zinc sulfate for 13 weeks. Animals were observed daily for clinical signs of toxicity and weighed weekly. Feed and water intake was measured twice per week. Prior to study termination, blood samples were collected and analyzed for hematological and biochemical parameters. Following necropsy, gross pathological and histopathological examinations were conducted on selected target organs and tissues. Organs weights were also determined.
Results	:	Although there were no obvious clinical signs of toxicity, four of 12 males in the high dose (30,000 ppm) group died or were killed *in extremis*. One female fed at this level also died. Histological findings in these animals revealed impairment of the urinary tract and regressive changes in the exocrine gland of the pancreas. Food consumption, water intake, and growth were depressed in the high dose groups, with the greatest effects seen in males. Male and female mice in the 30,000 ppm group showed moderately reduced levels of hematocrit and hemoglobin compared to controls; the leukocyte counts in these males were also decreased moderately. Mice of both sexes in the high dose groups showed a slight to moderate decrease in total protein, glucose and cholesterol, and a moderate to marked increase in alkaline phosphatase and urea nitrogen. Additional findings included depressed GPT levels in females, increased blood calcium levels in females, and increased GOT levels in males. Gross pathological changes in the high-dose animals included marked emaciation, ischemic discoloration of the kidney and thyroid, atrophy of the pancreas, edematous thickening of the upper small intestine, slight splenomegaly, and ulcers of the fore-stomach. Histopathological lesions were observed in the pancreas (swollen nuclei, necrosis of acinar cells), upper intestine (proliferation of epithelial cells), fore-stomach (ulcerations), spleen (proliferation of erythropoietic immature cells), and kidney (regression of renal cortex in females).
Remark	:	Results were consistent with those in rats (see previous robust summary); however, the effects on mice were generally more severe at the same level (ppm) in the diet. Most likely this was due to the much higher dose levels of zinc sulfate in mice compared to rats (approximately double on a mg/kg/d basis) due to their smaller size and greater relative food intake.
Reliability	:	2 (reliable with restrictions): Comparable to guideline study with adequate documentation.
Reference	:	Maita, K., M. Hirano, K. Mitsumori, K. Takahashi, and Y. Shirasu. 1981. Subacute toxicity studies with zinc sulfate in mice and rats. . J. Pesticide Sci., 6: 327-336.

5.5 GENETIC TOXICITY - MUTAGENICITY

Type	:	Mutagenicity
Guideline/method	:	Rec-assay
System of testing	:	Bacteria *in vitro*
Species	:	*Bacillus subtilis*
Strain	:	H17 (rec+) and M45 (rec-)
Test concentrations	:	0.05 M
Cytotoxic concentr.	:	Not determined
Metabolic activation	:	No
Year	:	1975
GLP	:	No
Test substance	:	Zinc chloride
Method	:	Kada et al., 1972. Mutation Res., 16:165-174.
Method detail	:	An 0.05 ml aliquot of a 0.05 M zinc chloride solution was tested.
Result	:	At the concentration tested, there was no inhibition of either the rec+ or rec- strain of *Bacillus subtilis*, suggesting that zinc chloride did not cause DNA damage.
Remark	:	In 11 separate in vitro studies with zinc chloride or zinc sulfate, negative results were reported with the exception of two ambiguous results and one weakly positive result. (Risk Assessment for Zinc Metal, 2001, draft). Genotoxicity studies in a variety of test systems have failed to provide evidence for mutagenicity of zinc. However, there are indications of weak clastogenicity following zinc exposure (ATSDR, 2003 Draft Toxicological Profile for Zinc). The results of short-term genotoxicity assays for zinc are equivocal. Responses in mutagenicity assays are thought to depend on the form (e.g., inorganic or organic salt) of the zinc tested (U.S. EPA, 2003, Integrated Risk Information System (IRIS) Summary for Zinc and Compounds).
Reliability	:	2 (reliable with restrictions): Acceptable study with adequate documentation.
Reference	:	Nisioka, H. 1975. Mutagenic activities of metal compounds in bacteria. Mutation Res., 31: 185-189.

Type	:	Mutagenicity
Guideline/method	:	Microscreen assay
System of testing	:	Bacteria *in vitro*
Species	:	*Escherichia coli*
Strain	:	$WP_s(\lambda)$
Test concentrations	:	Not specified
Cytotoxic concentr.	:	>1 mM
Metabolic activation	:	No
Year	:	1987
GLP	:	No
Test substance	:	Zinc chloride
Method	:	Rossman et al., 1984. Environ. Mut., 6:59.
Method detail	:	
Result	:	Negative for Trp+ reversion, λ Prophage induction and WP2 comutagenenesis
Remark	:	
Reliability	:	2 (reliable with restrictions): Comparable to guideline study with adequate documentation.
Reference	:	Rossman, T.G., J.T. Zelikoff, S. Agarwal, and T.J. Kneip. 1987. Genetic toxicology of metal compounds: an examination of appropriate cellular

models. Toxicol. Environ. Chem., 14:251-262.

Type	:	Mutagenicity
Guideline/method	:	L5178Y/TK somatic cell point mutation assay
System of testing	:	Cultured mouse lymphoma cells – *in vitro*
Species	:	Mouse
Strain	:	L5178/TK$^{+/-}$
Test concentrations	:	1.21 – 12.13 μg/ml
Cytotoxic concentr.	:	Not determined
Metabolic activation	:	No
Year	:	1980
GLP	:	No
Test substance	:	Zinc chloride
Method	:	Clive et al., 1972. Mutation Res., 16:77-87.
Method detail	:	
Result	:	Zinc chloride was not mutagenic under the test conditions.
Remark	:	
Reliability	:	2 (reliable with restrictions): Acceptable study with adequate documentation.
Reference	:	Amacher, D.E. and S.C. Paillet. 1980. Induction of trifluorothymidine-resistant mutants by metal ions in L5178Y/TK+/- cells. Mutation Res., 78: 279-288.

5.6 GENETIC TOXICITY - CLASTOGENICITY

Type	:	Chromosomal aberrations in bone marrow cells
Guideline/method	:	*In vivo*
Species	:	Mouse
Strain	:	C57B1
Sex	:	Male
Route of admin.	:	Diet
Exposure period	:	One month
Doses	:	0.5% Zn in feed
Year	:	1979
GLP	:	No
Test substance	:	Zinc chloride
Method	:	
Method detail	:	8-week-old mice kept on a normal (1.1% calcium) or low-calcium (0.03%) diet were exposed for one month to zinc chloride (0.5% Zn). After test termination, the bone marrow cells (50 metaphases/animal) from 10 animals were assayed for chromosomal aberrations.
Result	:	The body weights of mice fed zinc in the diet, either with normal or low calcium, were significantly reduced compared to their respective controls. Zinc treatment caused a significant increase in cells with structural aberrations (primarily dicentric chromosomes) for mice on low calcium diets. Aberrations were also increased in Zn-treated mice with normal calcium diets, but the increase was not statistically significant.
Remark	:	Studies on the induction of chromosome aberrations in bone marrow cells harvested from animals exposed to zinc compounds have yielded equivocal results. Increased aberrations have been seen in rats after oral exposure to zinc chloride in water (249 mg/L for 14 days) and in mice given intraperitoneal injections of zinc chloride (2-5 mg/kg as zinc chloride). In contrast, other studies have produced negative findings or have suggested that the induction of aberrations is contingent upon concomitant calcium deficiency. Negative results have been reported in the mouse micronucleus test (i.p. injection of zinc sulfate) and in the dominant lethal mutation assay

with mice (i.p. injection of zinc chloride at 15 mg/kg). (WHO, 2001, Environmental Health Criteria 221, Zinc).

Reliability : 2 (reliable with restrictions): Acceptable study with adequate documentation.

Reference : G. Deknudt and G.B. Gerber. 1979. chromosomal aberrations in bone-marrow cells of mice given a normal or a calcium-deficient diet supplemented with various heavy metals. Mutation Res., 68:163-168.

5.8.2 DEVELOPMENTAL TOXICITY

Type	:	Teratogenicity
Guideline	:	Not specified
Species	:	Mouse
Strain	:	CF-1 albino
Sex	:	Female
Route of admin.	:	Intraperitoneal
Exposure period	:	Day 8, 9, 10, or 11 of gestation
Frequency of treatment	:	Single dose
Duration of test	:	To gestation Day 18
Doses	:	12.5, 20.5, or 25 mg $ZnCl_2$/kg
Control group	:	Yes (distilled water only)
NOAEL maternal tox.	:	12.5 mg $ZnCl_2$/kg
NOAEL teratogen.	:	12.5 mg $ZnCl_2$/kg
Other	:	
Other	:	
Other	:	
Year	:	1977
GLP	:	No
Test substance	:	Zinc chloride
Method	:	
Method detail	:	Gravid female mice were given an i.p. injection of either 12.5, 20.5 or 25 mg $ZnCl_2$/kg on Day 8, 9, 10, or 11 of gestation. Following the respective treatments, the mice were allowed to continue their gestation uninterrupted until Day 18 (one day prior to expected delivery), when each pregnant mouse was sacrificed. The number of fetuses and resorption sites (metrial glands) was determined and recorded. Each fetus was then weighed, sexed, and examined for external defects. Every other fetus was processed for skeletal examination by the method of Staples and Schnell (1964).
Result	:	Zinc chloride, when administered in doses of 20.5 and 25 mg/kg, produced significant incidences of skeletal defects in fetuses as compared to those observed in the water-treated group on Day 11. Both doses also resulted in mortality of gravid females. The majority of defects involved the rib cage and included a ripple rib anomaly; however, the zinc salt failed to produce a significant incidence of soft tissue anomalies with either treatment regimen. As the dosage of $ZnCl_2$ was reduced, maternal and fetal toxicity, relative fetal weights, and the incidences of skeletal anomalies were correspondingly decreased. Maternal toxicity and incidences of skeletal anomalies were greatest when doses were administered on Day 11 of gestation. Zinc chloride, given at 12.5 mg/kg on day 11 of gestation, induced nonsignificant incidences of both skeletal and soft tissue defects compared to controls. No deaths were observed in the gravid females and no ripple ribs were observed in their fetuses.
Remark	:	Developmental toxicity data for several zinc compounds are available. Second-generation mice (from mothers fed zinc carbonate) exposed to high doses of zinc throughout the gestation, lactation, and postweaning periods had elevated levels of zinc in their bones, decreased blood copper levels, lowered hematocrit values and reduced body weights. The offspring of

pregnant rats fed zinc carbonate (500 mg Zn/kg) did not demonstrate any increase in the incidence of malformations. (WHO, 2001, Environmental Health Criteria 221, Zinc). Several developmental toxicity studies have been conducted with zinc sulfate on mice, rats, hamsters and rabbits, in general accordance with OECD Guideline 414; however, the form of the zinc sulfate was not specified. Depending upon the form that was used, the calculated NOAEL values ranged from 6.8 mg Zn/kg bw for the mouse to 35.2 mg Zn/kg bw for the hamster. (Risk Assessment for Zinc Metal, 2001, draft).

Reliability : 2 (reliable with restrictions): Comparable to guideline study with adequate documentation.

Reference : Chang, C-H., D.E. Mann, and R.F. Gautieri. 1977. Teratogenicity of zinc chloride, 1,10-phenanthroline, and a zinc-1,10-phenanthroline complex in mice. J. Pharm. Sci., 66:1755-1758.

5.8.3 TOXICITY TO REPRODUCTION

Type	:	Single-generation pilot breeding study
Guideline	:	Not specified
In vitro/in vivo	:	In vivo
Species	:	Rat
Strain	:	Sprague-Dawley SDTM
Sex	:	Both male and female
Route of admin.	:	Oral gavage
Exposure period	:	Males: Prior to cohabitation (77 d) and during cohabitation (21 d) Females: Prior to cohabitation (77 d), during cohabitation (21 d), and throughout gestation (21 d) and lactation (21 d).
Frequency of treatment	:	7 days/week
Duration of test	:	140 days (20 wk)
Doses	:	0, 7.5, 15, and 30 mg $ZnCl_2$/kg/d
Control group	:	Yes
Year	:	2001
GLP	:	No
Test substance	:	Zinc chloride
Method	:	Single generation breeding study
Method detail	:	Male and female rats (10 each per treatment) were administered 0.0, 7.5, 15.0, or 30.0 $ZnCl_2$ for 77 days prior to mating. At the end of the pre-mating period, males and females were paired within the same dose groups. Dosing was continued for both sexes throughout mating. All males were euthanized at the conclusion of mating, weighed, necropsied, and examined for morphological changes. Dosing was continued for females throughout gestation and lactation. Pregnant females were allowed to deliver their offspring naturally. Litter sizes were standardized on day 4 after birth to 4 of each sex. At day 21 of lactation, all F_0 females were sacrificed, necropsied, and examined for morphological changes. The evaluation of reproductive performance included fertility, viability index, weaning index, litter size, and the body weight of pups on days 0, 4, 7, 14, and 21 of lactation.
Results	:	The fertility indices in all dose groups were significantly lower than in the control group, but did not show a dose-response relationship. Pup viability indices on days 0 and 4 for the high-dose group were significantly lower than those of the control group. The body weights of pups in the highest dose group on days 14 and 21 were significantly lower than those in the control group. There were no effects on weaning indices or sex ratios. Overall, the results suggested that $ZnCl_2$ has only mild effects on rat reproductive performance up to 30 mg/kg/d. In addition, there were no significant treatment-related changes observed in any of the clinical

pathology parameters that were evaluated. All histopathologic effects related to treatment were mild. Those in the reproductive organs were confined to males only and according to the authors probably precluded any adverse effects upon reproduction.

Remark : The effects on reproduction of other zinc compounds have also been studied. The LOAEL for serious reproductive effects in female rats was 200 and 250 mg Zn/kg/d from exposure to zinc sulfate and zinc carbonate, respectively, in the diet. (ATSDR, 2003, Draft Toxicological Profile for Zinc).

Reliability : 2 (reliable with restrictions): Comparable to guideline study with adequate documentation.

Reference : Khan, A.T., A. Atkinson, T.C. Graham, M. Green, S. Ali, S.J. Thompson, and K.F. Shireen. 2001. Effects of low levels of zinc on reproductive performance of rats. Environ. Sci. (Tokyo), 8(4): 367-381.

Type : Sperm chromatin structure
Guideline : None
In vitro/in vivo : In vivo
Species : Rat
Strain : Sprague-Dawley
Sex : Male
Route of admin. : Diet
Exposure period : 8 weeks
Frequency of treatment : Continuous
Duration of test : 8 weeks
Doses : 4, 12, or 500 mg Zn/kg of diet (ppm)
Control group : No
Year : 1993
GLP : No
Test substance : Zinc chloride
Method :
Method detail : Three-week old male rats (10 per group) were fed experimental diets with concentrations of zinc considered to be deficient (4 mg/kg), adequate (12 mg/kg) or excessive (500 mg/kg). After 8 weeks of feeding, animals were sacrificed to obtain testicular germ cells and epididymal sperm. Flow-cytometric procedures were used to determine effects on rat testicular development, including integrity of caudal epididymal sperm chromatin structure defined as the susceptibility of DNA to denaturation *in situ*.

Results : Rats fed the zinc deficient (4 ppm) diet demonstrated significant deviations in the ratio of testicular cell types present, including a reduction of S phase and total haploid cells. In addition, approximately 50% of epididymal sperm has a significant decrease in resistance to DNA denaturation *in situ*. Rats fed either a Zn-adequate or Zn-excess diet did not demonstrate an abnormal testicular cell type ratio. Excess Zn had a negative effect on chromatin structure, but much less than that of Zn deficiency.

Remark : Rats fed zinc chloride daily over an 8 week period demonstrated altered sperm chromatin structure with a LOAEL of 25 mg Zn/kg/d.

Reliability : 2 (reliable with restrictions): Comparable to guideline study with adequate documentation.

Reference : Evenson, D.P., R.J. Emerick, L.K. Jost, H. Kayongo-Male, and S.R. Stewart. 1993. Zinc-silicon interactions influencing sperm chromatin integrity and testicular cell development in the rat as measured by flow cytometry. J. Anim. Sci., 71:955-962.

6.0 OTHER INFORMATION

6.1 Carcinogenicity

No adequate experimental evidence has been found to indicate that zinc salts administered orally or parenterally are tumorigenic. (WHO, 2001, Environmental Health Criteria 221, Zinc).